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ORIGINAL ARTICLE

# Catheter-based radiofrequency renal sympathetic denervation for resistant hypertension; initial Egyptian experience



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## KEYWORDS

Sympathetic;  
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**Abstract** *Objectives:* To evaluate the feasibility, efficacy, and safety of catheter-based radiofrequency renal sympathetic denervation for treatment of resistant hypertension.

*Background:* In a subpopulation of patients with essential hypertension, therapeutic targets are not met, despite the use of multiple types of medication. In this paper we describe our first experience with a novel percutaneous treatment modality using renal artery radiofrequency (RF) ablation.

*Methods:* Thirty patients with essential hypertension unresponsive to at least three types of antihypertensive medical therapy (baseline office systolic blood pressure  $\geq 160$  mmHg) were selected between March and September 2012 and received percutaneous RF ablation. Patients were followed up for 6 months after treatment. The primary effectiveness endpoint was change in seated office-based measurement of systolic blood pressure at 6 months. Another thirty patients were taken as control.

*Results:* A reduction of mean office blood pressure was seen from  $170/102 \pm 9/5$  mmHg at baseline to  $151/91 \pm 8/6$  mmHg at 6 months follow-up ( $p = 0.001$ ). Also, we noted a significant decrease in plasma renin activity ( $3.66 \pm 0.64$  versus  $3.37 \pm 0.47$  ng/mL/h;  $p = 0.003$ ). No periprocedural complications, adverse events or change in renal function were noted during follow-up.

*Conclusion:* Catheter-based renal denervation seems an attractive minimally invasive treatment option in patients with resistant hypertension, with a low risk of serious adverse events.

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## 1. Introduction

Successful treatment of raised blood pressure has proven elusive despite availability of various drugs, combination pharmaceutical products, and resources to assist patients' adherence and lifestyle changes. In about half of hypertensive patients, blood pressure remains higher than accepted treatment targets despite the broad availability of effective pharmaceutical agents.<sup>1,2</sup>

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Thus, the development of new approaches for the management of hypertension is a priority. These considerations are especially relevant to patients with drug-resistant hypertension and/or patients with severe intolerance to medication.

Renal sympathetic nerves contribute to development and perpetuation of hypertension, and sympathetic outflow to the kidneys is activated in patients with essential hypertension.<sup>3</sup> Efferent sympathetic outflow stimulates renin release, increases tubular sodium reabsorption, and reduces renal blood flow.<sup>4</sup> Afferent signals from the kidney modulate central sympathetic outflow and thereby directly contribute to neurogenic hypertension.<sup>5–7</sup>

Radical surgical methods for sympathetic denervation have been successful in lowering blood pressure in severely hypertensive patients. However, these methods were associated with high perioperative morbidity and even mortality and also long-term complications.<sup>4</sup>

Recently, a percutaneous, catheter-based approach using radiofrequency energy (RF) was developed to disrupt renal sympathetic nerves. This resulted in no severe (long-term) vascular or renal injury. Importantly, catheter-based renal nerve ablation was associated with a significant reduction in both systolic and diastolic blood pressure on top of maximal medical therapy, which persisted throughout 12 months follow-up in the first-in-man study.<sup>5</sup>

The Symplicity HTN-2 Trial was recently published, which was the first randomised controlled study using this technique of renal denervation, confirming the findings of the first-in man study.<sup>6</sup>

Here, we report the results of the Egyptian experience regarding this novel treatment modality.

## 2. Materials and methods

### 2.1. Study design and patients

Patients were eligible if they have an office systolic blood pressure of 160 mmHg or more, despite being compliant with at least three antihypertensive drugs, or confirmed intolerance to medication. Blood pressure measurements were performed in a seated position in at least two subsequent visits in both arms. Blood pressure check was performed before intervention and at 6 months follow-up.

Also, renal function and changes in plasma renin level were obtained at baseline and during follow-up.

The renal artery anatomy was considered suitable in case of a vessel diameter of  $\geq 4$  mm, no prior renal angioplasty/stenting and no significant stenosis or other abnormalities.

Exclusion criteria for this treatment modality were pregnancy, age below 18 years, patients with any known secondary cause of hypertension and a glomerular filtration rate estimated at  $< 45$  mL/min/1.73 m<sup>2</sup>. Also, patients with type 1 diabetes, haemodynamically significant valvular disease or implantable cardioverter defibrillators were excluded from intervention.

Thirty patients underwent renal denervation and another thirty patients with resistant hypertension were considered as control.

### 2.2. Procedure

The baseline activated clotting time (ACT) was determined, the renal artery was catheterized via standard femoral access,

and renal angiography was then performed, after which 70 mg/kg of heparin sodium was administered. When an ACT of 250–300 s had been achieved, a Symplicity electrode was introduced through a renal double-curve, left internal mammary artery, or renal short standard guiding catheter at least 6F in diameter. The radiopaque tip of the electrode was brought into contact with the endothelium, initially at the most distal point of the renal trunk.

When the impedance was stable we applied RF energy for 2 min, automatically regulated to 8 W with a maximum temperature of 70 °C. If the impedance value recorded at the time of RF application was too high, indicating the presence of calcium, the electrode was moved to a more favorable position. If the bifurcation was early, RF could be applied in the branches, provided they were of adequate diameter (i.e.,  $\geq 4$  mm).

A bilateral treatment of the renal arteries was performed with the use of series of 2-min RF energy deliveries along each artery, aiming at 4–6 treatment points per artery. These treatment points are made with a minimum of 5 mm distance in between and with a pullback from distal to proximal in a circumferential way. A control angiography was performed after the procedure.

### 2.3. Statistical analysis

We assessed continuous variables between groups, including the primary endpoint, with Student's two-sample *t* test unless otherwise specified. We compared categorical variables with Fisher's exact test. For within group paired data, a paired *t* test was used unless otherwise specified. A two-sided alpha level of 0.05 was used for all superiority testing. All statistical analyses were done using SPSS software statistical computer package version 16.

## 3. Results

The baseline characteristics of the patient groups are listed in Table 1. The mean time of the procedure (i.e. from puncture of the femoral artery to closure) was  $74 \pm 9$  min. Mean fluoroscopy time was  $14 \pm 5$  min. The ACT time achieved was  $288 \pm 44$  s. The mean use of contrast was  $208 \pm 35$  ml.

**Table 1** Baseline patient characteristics.

<i>Demographic information</i>	
Age, yrs	56 $\pm$ 6
Men, %	80
BMI, kg/m <sup>2</sup>	28.9 $\pm$ 3.3
<i>Relevant medical history</i>	
Duration of hypertension, yrs	9.8 $\pm$ 2
Diabetes mellitus	18(60%)
CAD	12(40%)
<i>Antihypertensive drugs</i>	
ACEI/ARB	28(93.3%)
Calcium channel blocker	28(93.3%)
B-blocker	22(73.3%)
Diuretic	30(100%)
$\alpha$ -blocker	2(6.7%)
Centrally acting drug	0(0%)

Values are mean  $\pm$  SD or *n* (%).

ACEI = angiotensin-converting enzyme inhibitor; CAD = coronary artery disease.

In total, an average of  $4.9 \pm 1$  RF ablations were performed in the left renal artery, and  $5.2 \pm 1$  RF ablations in the right renal artery. No patients showed endovascular damage at final angiography.

In general, there were no periprocedural (particularly access site) complications and/or complications during follow-up. No changes in medication were noted at 1-month follow-up. But, there was a significant increase in medications in the control group after 6 months;  $p = 0.004$  Fig. 1.

As shown in Fig. 2, after denervation, the systolic office blood pressure decreased from  $170 \pm 8$  mmHg at baseline to  $151 \pm 8$  mmHg at 6 months follow-up. This is a decrease of  $19 \pm 8$  mmHg ( $p = 0.001$ ). The diastolic blood pressure changed from  $102 \pm 5$  mmHg at baseline to  $91 \pm 6$  mmHg at 6 months (decrease of  $11 \pm 5$  mmHg;  $p = 0.001$ ). While in the control group, there was no significant decrease in blood pressure.

No significant change was noted in the serum creatinine level after the procedure ( $0.95 \pm 0.18$  mg/dL before compared with  $1.04 \pm 0.2$  mg/dL after 6 months;  $p = 0.234$ ). However, there was a statistically significant drop in the plasma rennin level at 6 months after denervation (from  $3.66 \pm 0.64$  to  $3.37 \pm 0.47$  ng/mL/h;  $p = 0.003$ ) compared with the control group (see Table 2).

#### 4. Discussion

Our first experience with renal sympathetic denervation, using a percutaneous approach, confirms the results of the previous proof-of-principle and recent randomized study, showing the safety and efficacy of this new treatment modality in daily clinical practice for patients with therapy resistant hypertension.<sup>5,6</sup>

The decrease of blood pressure achieved in our patient population is comparable with that achieved in the previous stud-

ies and most likely will be clinically relevant, although current guideline target values were not met in our patients with extreme hypertension (baseline blood pressure 180/110 mmHg).<sup>7</sup>

A recent meta-analysis by Law et al. showed that irrespective of the type of medication used, the incidence of coronary heart disease events was reduced by 22% after a systolic blood pressure reduction of 10 mmHg or a diastolic blood pressure reduction of 5 mmHg. Even more, the incidence of stroke was reduced by 41%.<sup>8</sup>

Assuming that the effects of renal denervation are as effective in reducing clinical events as a pharmacological approach for the treatment of hypertension, the observed blood pressure reduction of 19/8 mmHg in our patients will most likely be highly beneficial. The efficacy of this new treatment option should not only be present in the short term, but particularly during long-term follow-up.

Patients treated with this new technique approached the 6 month follow-up, and the blood pressure reductions observed appear to be sustained over this period, suggesting the absence of nerve fiber recovery, nerve fiber regrowth, or development of counter-regulatory blood pressure-elevating mechanisms.<sup>9</sup>

Besides efficacy, safety remains an equally important issue in a therapy for a certain disease. No adverse events were noted in our first patients periprocedurally and/or at follow-up. In the first cohort study performed in a multicentre setting, no renal artery stenosis occurred as verified using follow-up renal magnetic resonance angiogram at 6 months.<sup>5</sup>

Among all patients treated worldwide, a local dissection without sequelae was noted during the procedure in two patients, a few access site bleedings were reported, but no (long-term) side effects have been published up till now.<sup>6</sup> Particularly, no change in renal function has been noted.

There is accumulating preclinical and clinical evidence compelling for a primary role of renal sympathetic activation in the pathogenesis of hypertension as described in recent review articles.<sup>10,11</sup> A crosstalk between the central nervous system and the kidneys is present.

Blocking sympathetic nerves leading to the kidney ('efferent') will reverse fluid and salt retention. By blocking sympathetic nerves emanating from the kidney ('afferent'), renal denervation may also decrease the stimulation of other parts of the sympathetic nervous system, such as the heart and blood vessels, leading to an additional antihypertensive effect.

The earliest insight into the influence of intervention of the sympathetic nerve activity on renal function in hypertension is that of Claude Bernard in 1859.<sup>12</sup> He observed that by cutting

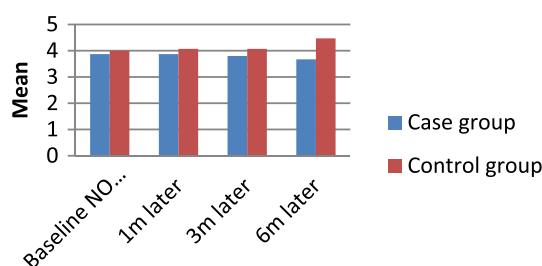


Figure 1 Medication number.

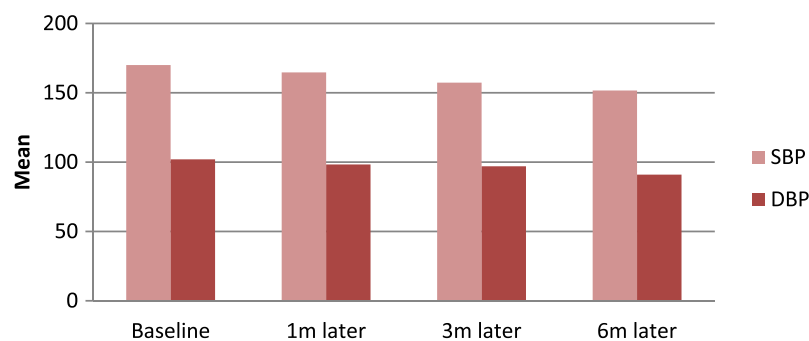


Figure 2 Blood pressure follow up after denervation.

**Table 2** shows the procedural characteristics.

	No. of ablations		Ablation duration (S)	Total RF (S)	Temp. max. (°C)	Power avg. (W)	Mean impedance (Ω)	Fluoroscopy time (min)
	Rt.	Lt.						
Average	5.2 ± 1	4.9 ± 1	25 ± 4	241 ± 88	39 ± 3	15 ± 3	16 ± 6	14 ± 5
Minimum	4	3	15	116	35	10	9	8
Maximum	8	6	30	389	43	18	24	23

the greater splanchnic nerve, he caused an increased diuresis, whereas electrical renal sympathetic nerve stimulation produced a reduced diuresis.

However, the surgical approach of (non-specific) renal denervation coincided with severe side effects as observed in studies from the 1930s using surgical denervation of the sympathetic system of the thoracico-lumbar region and has therefore been abandoned.<sup>13,14</sup> Using the catheter-based renal denervation in patients as described in this paper, we may have overcome these side effects of nonspecific denervation of the lumbar region.<sup>15</sup>

Pathophysiological proof of concept of the denervation of the renal artery has also been shown in a small subset of patients.<sup>16,17</sup> Schlaich et al. demonstrated that the so called nor-epinephrine spillover resulted in a decrease of 40–50%, which was accompanied by halving of rennin activity and an increase in renal plasma flow. In our population, a decrease in plasma rennin was noted.

For future therapeutic application of sympathetic denervation of the renal arteries, further research is needed to identify groups of patients who might benefit from this intervention. In this light, searching for efficacy in patients with, for instance, chronic kidney disease, patients with heart failure, diabetes and obesity will be interesting. Also, studies in milder forms of essential hypertension should be the next goal of research using this percutaneous technique. Hereby, hard endpoint studies are warranted to prove the value of this new percutaneous technique in daily clinical practice.

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